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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/519,959	03/07/2000	Nancy Carrasco	96700/488	9663

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	22

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/519,959	CARRASCO ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,8,9,29 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,8,9,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed on December 20, 2002 in Paper No. 20 is acknoweledged and has been entered. Claims 4, 5, and 7 have been canceled. Claims 1, 6, 8, 9, and 29 have been amended. Claim 30 has been added.

2. Claims 1, 2, 6, 8, 9, 29, and 30 are pending in the application and are currently under prosecution.

Grounds of Claim Rejections Withdrawn

3. Unless specifically reiterated below, the grounds of rejection set forth in previous Office action have been withdrawn.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 2, 6, 8, 9, 29, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cancroft, et al (*Radiology* **106**: 441-444, 1973), as evidenced by Socolow, et al (*Endocrinology* **80**: 337-344, 1967), in view of Eskin, et al (*Obstetrics and Gynecology* **44**: 398-402, 1974), Spitzweg, et al (*Journal of Clinical Endocrinology* **83**: 1746-1751, 1998) and Jhiang, et al (*Endocrinology* **139**: 4416-4419, 1998).

Cancroft, et al teach a method for diagnosing breast cancer in a subject, said method comprising scintigraphic imaging of tumor masses by administering ^{99m}Tc-pertechnetate to the subject (abstract). Cancroft, et al disclose that "in patient A.Y., a lesion of the left breast diagnosed as malignant on mammography was readily observed on scintigraphy" (page 443, column 1). While Cancroft, et at teach that the mechanism

of ^{99m}Tc-pertechnetate concentration in malignant breast masses is not clear, it is an inherent feature of ^{99m}Tc-pertechnetate to concentrate in the malignant breast masses by a mechanism involving its selective uptake by NIS, as evidenced by Socolow, et al and Spitzweg, et al. In the method of Cancroft, et al, the level of ^{99m}Tc-pertechnetate taken up by a cancer cells reflects the level of expression in the cells of mgNIS, which is responsible for the uptake of ^{99m}Tc-pertechnetate. Therefore, the level of radioactivity detected in the cells is a measure of the level of mgNIS expression in the subject's breast cancer cells; thus, the diagnostic method of Cancroft, et al intrinsically detects the expression of mgNIS in the cancer cells.

However, Cancroft, et al do not expressly disclose that the expression of mgNIS can also be measured using either a detectably labeled anti-mgNIS antibody (e.g., a Western blot analysis) or a detectably labeled nucleic acid probe that hybridizes to the mRNA molecule that encodes mgNIS (e.g., a Northern blot analysis).

Socolow, et al provide evidence that ^{99m}Tc-pertechnetate is selectively taken up by the thyroid gland (abstract) by a mechanism that resembles the mechanism by which radioiodide is taken up by the cells.

Eskin, et al teach that "pilot studies show that ^{131}I concentration in biopsied human breast tissues with carcinoma or dysplasia is higher than in histologically normal tissues from the same patient" (abstract). Eskin, et al conclude that the use of the diagnostic technique has several advantages (page 402, column 1), because of the fact that breast cancer takes up a greater amount of radioiodide.

Spitzweg, et al teach a method for detecting the expression of human NIS in tissue samples acquired from a subject (abstract) by Northern blot analysis, which utilizes a nucleic acid probe that specifically hybridizes to mRNA encoding human NIS (page 1747, column 1). Spitzweg, et al also teach that the ability of thyroid tissue to selectively concentrate radioiodide is dependent upon the activity of NIS, which is commonly expressed in breast tissue also. Specifically, Spitzweg, et al teach that "the nucleotide sequences of hNIS cDNA derived from parotid gland, mammary gland, and gastric mucosa revealed **full id ntity with th rec ntly published human thyroid-d riv d NIS cDNA s quence**" (emphasis added) (abstract). Spitzweg, et al conclude,

"our detection of significant quantities of hNIS [human sodium/iodide symporter] gene expression in thyroid gland, salivary glands, thymus, pituitary gland, pancreas, testis, mammary gland, and gastric mucosa, and lower degrees of NIS gene expression in prostate, ovary, adrenal gland, lung, heart, and nasopharyngeal mucosa suggests that iodide transport in some of these tissues may be **a specific property conferred by the expression of NIS**" (emphasis added) (page 1750, column 1).

Jhiang, et al teach the immunohistochemical analysis of human sodium/iodide symporter (NIS) expression in tissue samples acquired from a subject (abstract). More specifically, Jhiang, et al teach that an antibody that is detectably labeled, which specifically binds to human NIS, can be used in Western blot analysis of membrane fractions from cells isolated from a subject (page 4417, column 1). Furthermore, Jhiang, et al teach that the antibody can also be used to stain frozen tissue sections and paraffin-embedded tissue sections acquired by patient biopsy (page 4417, column 1-2). Clearly, both of the methods can be used to detect the expression of human NIS in the cells of a subject.

The human NIS to which the prior art antibody binds appears to be the same as mgNIS of the instant claims, absent a showing of unobvious differences. By the same token, it appears that the prior art nucleic acid probe hybridizes to the same nucleic acid molecule encoding mgNIS of the instant claims, absent a showing of unobvious differences. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed antibodies or probes are functionally different than those taught by the prior art and to establish patentable differences.

Accordingly, in view of the teachings of Spitzweg, et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to identify the presence of breast tissue that expresses relatively higher levels of mgNIS by either the method of Jhiang, et al or Spitzweg, et al, because Cancroft, et al teaches

that a method that detects the differential concentration of ^{99m}Tc-pertechnetate in breast cancer cells is diagnostic of breast cancer and because Eskin, et al teaches that breast cancer cells concentrate higher amounts of radioiodide than histologically normal breast tissue. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the methods of either Jhiang, et al or Spitzweg, et al with the diagnostic method of Cancroft, et al to confirm the diagnosis of breast cancer in the subject by an analysis of the level of mgNIS expression in biopsied tissue, because using a second reliable diagnostic method can prevent a misdiagnosis. It also would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the antibody of Jhiang, et al in a modification of the diagnostic method of Cancroft, et al, because the detectably labeled anti-mgNIS antibody also can be used to specifically and selectively target cancer cells that express mgNIS. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to modify the method of Cancroft, et al by using the antibody of Jhiang, et al to confirm the diagnosis of breast cancer in a subject using a second reliable method, in order to avoid a misdiagnosis.

Conclusion

6. No claims are allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
March 24, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600